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Step-Like DRL Schedule Change Effects on Blood Chemistry, Leukocytes and Tissue in Rats[1]

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PERSINGER, M. A., N. J. CARREY, G. F. LAFRENIÈRE AND A. MAZZUCHIN. *Step-like DRL schedule change effects on blood chemistry, leukocytes and tissue in rats.* PHYSIOL. BEHAV. 21(6) 899–904, 1978.—Male albino rats maintained at 80% free-feed body weight were trained daily for two weeks on DRL 6-sec schedules and either suddenly shifted to DRL 12-sec schedules or maintained on DRL 6-sec. Within 30 min, 1 day, 3 days or 7 days after the step-like schedule change, the rats were killed along with ad lib food controls. Wet tissue weights for adrenals, spleens, testicles and pituitaries were taken and 20 different blood serum constitutents were measured automatically on a SMAC unit. Although the rats that had been shifted from the DRL 6-sec to DRL 12-sec condition demonstrated the usual marked elevations in response/reinforcement ratios, only alkaline phosphatase, SGOT and relative blood lymphocyte numbers differed significantly from the DRL 6-sec controls; tissue weight differences were not apparent. Highly significant differences existed between the 80% body weight, DRL tested rats and the non-tested, ad lib controls for: glucose, blood urea nitrogen, chloride, carbon dioxide, calcium, alkaline phosphatase, SGPT, triglycerides, relative testicle weights, absolute spleen weights, and body weight.

Rat Blood chemistry Food deprivation Schedule change Wet tissue weights Inhibition DRL schedule Operant conditioning Leukocytes

THE organism can be viewed as a locus of behaviors within which a number of response systems (somatic, autonomic, immunological, biochemical, etc.) are related in a probabilistic manner. When control systems theory is applied, one predicts that sudden changes in input demands to this locus should initiate periods of instability and adjustment throughout the response matrices. Sudden and maintained changes in basic physicochemical parameters, such as temperature, can elicit changes in behavioral, biological and biochemical response systems. In recent years, evidence has accumulated that mere modifications in reinforcement patterns, especially sudden and protracted changes (step-like demands) can initiate not only behavioral perturbations but alterations in physiochemical and immunological stability as well.

According to the control systems applications of Halasz [2,3], one would expect both immediate and long-term effects of sudden schedule changes. Immediate (within 40 min) eosinopenia was found in rats suddenly changed from a fixed ratio 50 (FR 50) to a FR 125 reinforcement schedule [7] while elevations in plasma corticosterone were found [1] following CRF (continuous reinforcement) extinction (another form of step-change in schedule demands). Long-term consequences of reinforcement schedule changes would be expected as well; qualitatively, the lag-time and amplitude of these effects should be a function of the response duration, interresponse time and the relative amount of total response time emitted on that particular schedule.

Long-term effects of reinforcement changes, per se, have not been investigated experimentally. However, sudden changes in life styles, such as divorces, promotions, end of school terms, etc., which can be considered step-like changes in complex reinforcement schedules, are known to be correlated with later onset of disease [5]; the severity and likelihood of disease appear related in a linear-like manner to the number of life style changes within a particular time increment (e.g., a year). In fact, sudden changes in reinforcement schedules that comprise a major portion of a human organism's response profile, e.g., the death of a spouse, can be associated with elevations of corticosteroid excretion for more than a *year* after the change [4]. The immunosuppressive consequences of maintained elevations in corticosteroids have been suggested as a major contributor to the proliferation of disease processes, such as the herpes virus

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or carcinogens, normally accommodated by the body's immune system [6].

The present experiment was designed to measure the effects, if any, of sudden changes in inhibitory behavioral demands upon essential blood and organ systems in the rat as well as the time required to adjust to these demands. The DRL (differential reinforcement of low rates of responding) schedule was selected where reinforcement is contingent upon response postponement (inhibition). Rats that have been maintained on, for example, a DRL 6-sec schedule for 2 weeks but were then suddenly shifted to a DRL 12-sec contingency involving longer periods of response postponement required several sessions to adjust to the new demand. During this period, a number of clear behavioral and autonomic instabilities have been noted [8].

On the basis of previous experiments [9] and factor analysis of these results, we expected schedule change-induced increases in the following measures: blood serum triglycerides, SGOT (serum glutamic oxaloacetic transaminase), alkaline phosphatase, wet testicle weights, wet spleen weights and relative blood neutrophil numbers (with decreases in relative lymphocytes). Considering the relatively small amount of total organismic response time allocated to the schedule (only one 30 min session/24 hr), we did not expect (1) either highly significant and maintained increases in the above measurements or (2) alterations in blood glucose, electrolytes, albumin, protein and cholesterol or in adrenal weights and wet thymus weights or in relative eosinophil numbers. These measures usually change in response to more severe experimental manipulations of the rat such as surgery or prolonged food deprivation.

METHOD

Animals

In three experiments, 42, 100 day old male albino Wistar rats (*Rattus norvegicus*), obtained from Bio Breeding Laboratories of Canada, Limited, were used.

Procedure

Following arrival from the breeding laboratory, animals for a given experiment were maintained for 20 days in groups of three in automatic cages. At 92 days of age, 14 rats for a given experiment were separated into single cages and weighed. The body weights of 12 rats were reduced over an 8 day period to 80% of the free-feed weight. However, every week until the end of the experiment, the body weight of each rat was adjusted in order to compensate for normal weight gain due to growth. The remaining 2 rats in each experiment were not food deprived but served as ad lib controls.

The food deprived rats were assigned to one of 8 groups: step + 0 day, step + 1 day, step + 3 days, step + 7 days, step + 0 day control, step + 1 day control, step + 3 days control or step + 7 days control group. In each experiment, 2 rats were assigned to one of the step groups and the remaining rats were assigned to the control groups. When all three experiments were combined, there were 6 rats per step condition and 3 rats per control condition (plus the 6 ad lib controls).

Since all food deprived rats were to be exposed to two weeks of DRL 6-sec training before step operations were instituted and all rats were to be killed on one of two contiguous days, DRL 6-sec training was initiated at different times for the different groups. Thus the step + 7 day and step + 7 day control rats began DRL 6-sec training one week before the other groups that were killed on the day of the step change. The other groups of rats were delayed by the appropriate time before training began.

Rats were tested daily in one of two single lever Lafayette operant chambers housed in ventilated masking noise boxes; programming equipment was kept in another room. Following one day of CRF training to a criterion of 100 reinforcements (S^+s), the schedule was changed to a DRL 6-sec condition. In this situation, the animals had to postpone lever responding at least 6-sec in order to receive a 35 mg Noyes food pellet reward. If the time elapsed was less than 6-sec when the next lever press was emitted, then the next reward availability was postponed another 6-sec; there was no limited hold. Each rat was always tested in the same chamber by N.C. at the same time every day for 30 min until the end of the experiment; rats were tested between 0900 and 1400 hr local time. The number of responses (Rs), reinforcements (S^+s), and fecal boluses deposited in the chamber were recorded and the cumulative records were collected after each rat's daily run; at this time, the reinforcement apparatus were manually checked to insure function. When the grid floors and levers had been washed with 0.6% acetic acid and dried to attenuate olfactory cues, the rats were weighed, returned to the colony room and fed the appropriate amount to maintain 80% body weight. In order to eliminate possible running order effects (i.e., 6 pairs of rats over a 5 hr period), different step conditions or control conditions were counterbalanced with respect to time of day in the different experiments.

On what was called the step day, the schedule change rats were placed in the chambers, previously paired for 2 weeks with DRL 6-sec schedules, now programmed with DRL 12-sec schedules. Control rats were always exposed to the DRL 6-sec schedule for the entire experiment. On the kill day, the step + 0 day rats had just finished 30 min of the new DRL 12-sec schedule while the controls had just finished the usual DRL 6-sec; after the usual postsession procedures, the rats were taken to the kill room. On the kill day, the step + 1, + 3 and + 7 day rats had received 1, 3, or 7 days of the DRL 12-sec schedule while their controls had received the DRL 6-sec treatment; these rats had not been tested for 24 hr or fed for 23 hr and were taken directly from the colony room at their usual time, past the chamber room to the kill area. During the post-step days the daily food allocation had been increased for the step + 1, + 3 and + 7 days rats in order to compensate weight loss associated with fewer S^+s.

Each rat was carried to the kill room in its usual plastic shuttle cage by the animal tester who did not enter the kill area. Instead the rat was taken into the kill area by another person and decapitated within 20-sec. In each experiment, the 6 rats (always 4 step and 2 control) from Chamber A were killed on one day and the 6 rats (4 step and 2 controls from Chamber B) were killed the following day; consequently, only one rat was killed and processed at any given time. The ad lib controls were killed also on these days, one at the beginning of the session and one at the end.

Following decapitation, the blood was collected and allowed to stand for 15 min after which it was centrifuged at 3400 RPMs for 10 min. The serum was removed, centrifuged again and placed in coded test tubes and refrigerated overnight at 4°C. During the first 30 sec of blood collection, 3 thin blood smears were taken and later stained with the Wright's

procedure. Pituitaries, adrenals, spleens and testicles were removed quickly (all within 5 min) by M.A.P. and weighed within 30 sec by G.F.L. on a Mettler H18 analytical balance. A general necropsy was then conducted upon each rat. Macroscopic examinations were performed for: abdominal adipose tissue amounts, liver size and color, intestinal coloration, bloating and fecal matter, stomach contents and ulceration, lung color, blotching and texture, and general body condition. Evaluations were made on a 0 to 5 scale, with 3 as the normal reference. The blood serum was analyzed later under blind conditions on a Technicon SMAC (sequential multiple analyses computer) System (calibrated daily) by the technical group at Laurentian Hospital for albumin, protein, glucose, blood urea nitrogen (BUN), creatinine, sodium, potassium, chloride, carbon dioxide, uric acid (URICA), albumin/globulin ratios (A/G), calcium, phosphorous, lactate dehydrogenase (LDH), alkaline phosphatase (ALKPH), serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), bilirubin (total), cholesterol and triglycerides. A total of 100, white blood cells per slide were counted over a wide field for each rat's two best blood smears at 1000× under oil immersion; the average number of each cell type was converted into percent of total population. Analyses of covariance, variance, polynomial trends, *a posteriori* tests (Duncan's and Scheffe's) means and standard deviations for the various groups and conditions were completed on an IBM 360–40 computer using SPSS programs; sample results were checked against hand computations.

RESULTS

The means and standard deviations for the various behavioral measures from the animals' last test day before death are shown in Table 1. Two-way analyses of variance (ANOVAs) on these measures for the two conditions (step change and non-step) and the four days (0, 1, 3 and 7) demonstrated significant ($p<0.001$) differences between step change and non-step control groups for total S^+s, $F(1,28)=639.49$, and R/S^+ ratios ($F=22.57$) but no differences ($p>0.05$) for total Rs. A marginally significant difference in S^+ numbers existed across days ($F=3.59$; $p<0.05$). Further analyses indicated that only the step change rats significantly, $F(3,20)=3.77$, $p<0.05$, increased the numbers of S^+s over sessions following the step. The only significant interaction was for food consumption, $F(3,28)=4.41$, $p=0.01$. Further analyses showed that the interaction was primarily due to the increased food given to the post-step day 1, 3 and 7 rats, a planned part of the experimental design. In order to detect any possible initial group behavioral differences between step and control groups, Rs, S^+s, R/S^+s and chamber fecal bolus numbers for the first day of DRL 6-sec training (after CRF) and DRL 6-sec baseline (mean of 5 days before step day) as well as body weight and post-sessional food allocation for the baseline period were calculated. Two-way ANOVAs indicated no significant differences between groups for any of the measures.

Two-way ANOVAs for the two schedule conditions (DRL 6/12-sec step vs DRL 6-sec controls) and the four kill days (days 0, 1, 3 and 7) for the blood serum, tissue weight and circulating white blood cell measures demonstrated no significant ($p<0.05$) interactions. Consequently, the results are presented according to main effects:schedule conditions or kill days. Table 2 contains the means and standard deviations for the blood measures while Table 3 contains the means and standard deviations of the weight and leukocyte (only lymphocyte, neutrophil and eosinophil percentages were analyzed statistically since other types, e.g., monocytes, varied between 0 and 1/100) measures for the DRL 6/12-sec step and DRL 6-sec control groups. In addition, means and standard deviations for the blood and weight measures from the ad lib control group are also presented. Only the significant day differences will be presented below.

The two-way ANOVAs demonstrated that the rats that had received the sudden schedule change from DRL 6-sec to DRL 12-sec demonstrated significantly ($p<0.05$) elevated

TABLE 1

MEANS AND STANDARD DEVIATIONS (±) FOR LAST BEHAVIORAL MEASURES BEFORE KILL. N=24 FOR STEP GROUP AND N=12 FOR CONTROL GROUP

		Day 0	Day+1	Day+3	Day+7
Total Rs	Step	385 ± 72	359 ± 106	314 ± 109	282 ± 100
	Con	345 ± 49	346 ± 51	310 ± 37	332 ± 36
Total S^+	Step	18 ± 6	23 ± 8	37 ± 21	44 ± 19
	Con	162 ± 14	177 ± 25	163 ± 11	182 ± 18
R/S^+	Step	23 ± 9	17 ± 7	16 ± 15	9 ± 8
	Con	2 ± 0.5	2 ± 0.6	2 ± 0.2	2 ± 0.2
Number Boluses	Step	2 ± 2	1 ± 2	4 ± 3	1 ± 2
	Con	1 ± 2	1 ± 2	1 ± 2	1 ± 2
Post Session Food (g)	Step	8 ± 3	16 ± 6	16 ± 1	13 ± 3
	Con	8 ± 3	8 ± 2	7 ± 2	5 ± 2
Body Weight (g)	Step	344 ± 24	346 ± 44	349 ± 28	348 ± 27
	Con	346 ± 21	345 ± 23	338 ± 18	350 ± 32

* a vs b=$p\leq 0.05$ and a vs c=$p<0.001$: (1) according to main effect F values from two way ANOVAs for Step vs Control groups only and (2) according to Scheffe's set $p\leq 0.05$ for comparisons between step, control and ad lib groups, by one-way ANOVA.

TABLE 2

MEANS AND STANDARD DEVIATIONS (±) FOR 20 BLOOD SERUM MEASURES FROM RATS EXPOSED TO DRL 6/12 SEC SCHEDULE CHANGES, DRL 6 SEC CONTROL SCHEDULES OR AD LIB FOOD CONDITIONS*

Measure	DRL 6/12 sec Step (n=24)	DRL 6 sec Con (n=12)	Ad Lib Cons (n=6)
Albumin (g/dl)	4.4 ± 0.5	4.4 ± 0.5	4.4 ± 0.6
Protein (g/dl)	7.2 ± 0.3	7.4 ± 0.6	7.5 ± 0.4
Glucose (mg/dl)	142 ± 9[a]	140 ± 9[a]	160 ± 7[c]
BUN (mg/dl)	15.3 ± 2.4[a]	14.4 ± 3.1[a]	22.5 ± 6.2[c]
Creatine (mg/dl)	0.7 ± 0.1	0.7 ± 0.1	0.7 ± 0.1
Na (meq/L)	149 ± 4	150 ± 5	147 ± 5
K (meq/L)	7.9 ± 0.7	7.9 ± 1.3	8.4 ± 0.7
Cl (meq/L)	107 ± 3[a]	108 ± 3[a]	102 ± 2[b]
CO_2(meq/L)	21.5 ± 3.7[a]	20.6 ± 2.9[a]	27.0 ± 1.6[b]
Uric A (mg/dl)	1.3 ± 0.3	1.3 ± 0.2	1.2 ± 0.1
A/G	1.6 ± 0.4	1.6 ± 0.5	1.4 ± 0.3
Ca (mg/dl)	10.8 ± 0.4[a]	10.8 ± 0.4[a]	12.0 ± 0.4[b]
P (mg/dl)	8.2 ± 1.6	8.0 ± 1.6	8.2 ± 0.7
LDH (U/L)×10^1	150.3 ± 34.8	129.4 ± 37.0	150.6 ± 41.2
Alkaline Phosphatase (U/L)	201 ± 58[b]	160 ± 38[a]	334 ± 44[c]
SGOT (U/L)	189 ± 49[b]	158 ± 27[a]	184 ± 49
SGPT (U/L)	39.3 ± 8.8[a]	36.1 ± 9.3[a]	49.5 ± 7.2[b]
Cholesterol (ng/dl)	94.7 ± 12.9	91.6 ± 15.9	97.7 ± 12.0
Triglycerides (mg/dl)	61.1 ± 47.0[a]	49.0 ± 27.8[a]	196.0 ± 37.0[c]

* a vs b=$p \leq 0.05$ and a vs c=$p < 0.001$: (1) according to main effect F values from two way ANOVAs for Step vs Control groups only and (2) according to Scheffe's set $p \leq 0.05$ for comparisons bewteen step, control and ad lib groups, by one-way ANOVA.

alkaline phosphatase activity, F(1,28)=5.01, and SGOT activity, F(1,28)=5.01 relative to rats that had been maintained during the same periods on a DRL 6-sec schedule. SGPT activity displayed a similar but less intense change, F(1,28)=4.10, $p>0.05$. Step rats also displayed significantly decreased relative blood lymphocyte numbers, F(1,28)=4.94, $p<0.05$, and increased neutrophil numbers (F=3.70, $p>0.05$), relative to control rats. The differences between lymphocyte numbers between days 0, +1, +3 and +7 for the step rats only (76.5 ± 7.0, 79.2 ± 7.3, 85.0 ± 5.3 and 82.5 ± 5.2, respectively) were significant (Duncan's, $p=0.05$). The above measures remained statistically significant when co-varied for body weight. All other measures were not statistically significant between the two groups.

TABLE 3

MEANS AND STANDARD DEVIATIONS (±) FOR ABSOLUTE AND RELATIVE TISSUE WEIGHTS, BODY WEIGHTS AND RELATIVE LEUKOCYTE COUNTS FOR RATS EXPOSED TO EITHER THE SCHEDULE STEP CHANGE, SCHEDULE CONTROL OR AD LIB FOOD CONDITIONS*

	DRL 6/12 sec (n=24)	DRL 6 sec Con (n=12)	Ad Lib Controls (n=6)
Spleen (g)	0.56 ± 0.08[a]	0.55 ± 0.08[a]	0.79 ± 0.08[c]
Spleen (mg/g)	1.63 ± 0.21	1.60 ± 0.15	1.57 ± 0.16
Adrenal (mg)	43.9 ± 7.2	40.8 ± 4.5	45.6 ± 6.0
Adrenal (μg/g)	127 ± 18	118 ± 11	106 ± 19
Testicle (g)	3.65 ± 0.35	3.50 ± 0.37	3.94 ± 0.25
Testicle (mg/g)	10.6 ± 0.6[a]	10.1 ± 0.6[a]	8.95 ± 0.6[c]
Body (g)	346 ± 30[a]	345 ± 22[a]	440 ± 20[c]
Lymphocytes (%)	80.8 ± 6.7[a]	85.6 ± 5.8[b]	84.2 ± 4.5
Neutrophils (%)	18.2 ± 6.5	14.0 ± 5.6	15.3 ± 4
Eosinophils (%)	0.8 ± 0.7	0.4 ± 0.4	0.4 ± 0.7

* a vs b=$p \leq 0.05$ and a vs c=$p < 0.001$: (1) according to main effect F values from two way ANOVAs for Step vs Control groups only and (2) according to Scheffe's set $p \leq 0.05$ for comparisons between step, control and ad lib groups, by one-way ANOVA.

Two-way ANOVAs indicated that protein, $F(3,28)=4.14$, $p=0.01$, sodium ($F=3.94$, $p<0.05$) and cholesterol ($F=4.84$, $p=0.01$) levels significantly varied over days for step and non-step controls combined. The values for protein, sodium and cholesterol measures for day 0, +1 day, +3 days and +7 days were: 7.59 ± 0.55, 7.23 ± 0.33, 7.09 ± 0.23 and 7.16 ± 0.29 g/dl, 153 ± 3, 149 ± 3, 147 ± 3, and 149 ± 4 mEq/l, and 104 ± 12, 97 ± 14, 52 ± 38 and 49 ± 26 mg/dl, respectively. These measures remained significant when covariance for body weight was performed before the ANOVAs. *A posteriori t*-tests indicated that the major day effects were between day 0 values and the +3 and +7 day values. All other measures did not show significant day effects.

Trend (polynomial) analyses for only the step change rats over the four days indicated that significant amount of the alkaline phosphatase and triglyceride changes approximated quadratic terms, $F(1,20)=3.86$ and 4.73, respectively, while the latter measure also deviated significantly from the linear term, $F(2,20)=3.18$, $p=0.05$. The means and SDs for these measures over the 4 days were 170 ± 22, 203 ± 56, 229 ± 56, and 200 ± 56 U/L and 40 ± 20, 98 ± 71, 63 ± 42, and 43 ± 18 mg/dl, respectively. The control rats displayed no quadratic trends. Separate one-way ANOVAs for possible daily test sequence (n=6), experiment number (n=3) or test chamber (n=2) differences were not significant for any of the measures.

One-way ANOVAs between step change combined, control combined, and ad lib food controls for all blood and tissue measures demonstrated significant differences in glucose, $F(2,39)=10.67$, $p<0.001$, BUN ($F=13.21$, $p<0.001$), chloride ($F=7.42$, $p=0.001$), CO_2 ($F=8.45$, $p=0.001$), calcium ($F=17.70$, $p<0.001$), ALKPH ($F=23.97$, $p<0.001$), SGPT ($F=4.76$, $p=0.01$), triglycerides ($F=29.32$, $p<0.001$), absolute spleen ($F=14.84$, $p<0.001$), relative testicle weights ($F=18.76$, $p<0.001$) and body weight ($F=31.70$, $p<0.001$) measures. In all these measures, except the ALKPH and SGOT activity, the significant differences were only between the food-deprived rats combined (step and non-step) and ad lib controls, according to *a posteriori* tests (Scheffe's set $p<0.05$).

Post mortem results demonstrated no significant differences between groups except for primary experimental manipulations, such as Noyes pellet mush within the stomachs of rats that had just been removed from the chamber or large amounts of abdominal adipose tissue for the ad lib controls. In general, the rats appeared normal within the constraints of 80% food deprivation.

DISCUSSION

The present study has demonstrated that rats maintained at adjusted 80% body weights and tested daily on DRL 6-sec schedules do not demonstrate intense or major alterations in their blood and wet tissue weight systems when suddenly shifted to a DRL 12-sec schedule, either immediately or within 7 days, even though gross perturbations in response/reinforcement ratios were apparent. The blood measures (alkaline phosphatase activity, SGOT activity and relative lymphocyte numbers) that were influenced by the schedule change were only marginally significant statistically. Polynomial analyses indicated that only alkaline phosphatase activity and triglyceride levels demonstrated a marginal non-linear relationship across post-step adjustment days, suggesting that small elevations and adjustments to the new schedule demand occurred in these measures.

No doubt the most significant effects occurred between the ad lib controls and the 80% body weight rats. The significant alterations in blood serum glucose, urea nitrogen, chloride, calcium, alkaline phosphatase, GPT and triglycerides and tissue weights noted between these groups have been observed by us to be frequently sensitive to stress factors, e.g., differences in cage density, room temperature, or to the more obvious correlations of body weight, e.g., the amount of abdominal adipose tissue. The food factor appears to be responsible for the day effects since the more significant differences occurred between the day 0 rats (killed with food in their stomachs) and the other rats (last fed 23 hr before death). From the perspective of rat physiology, one is surprised at the stability of the many blood measures that did not change despite the effects of 3 to 4 weeks of relative food deprivation.

The relative paucity of significant blood and tissue changes following alterations in a reinforcement schedule known to produce autonomic or emotional behavior may have involved at least three variables. First, the effects of food deprivation altered not only the measures influenced by the step change but other measures as well; the significant food deprivation effects may have altered the minimum-maximum response range available to the organism. Secondly, one consequences of the schedule change should have been a post-step period of adjustment oscillations, typified by larger measurement variabilities relative to non change rats, thus masking any weak effects. In the present study, there were no extraordinary differences between step and control group standard deviations, although the triglyceride, SGOT and alkaline phosphatase deviations were in the expected direction.

A final possibility may be related to the schedule itself. Although sudden DRL changes do alter R/S^+ ratios for weeks (in this study the step animals had still not adjusted to pre-step levels), the total number of responses displayed by the step rats did not vary from the controls which maintained the DRL 6-sec R/S^+ ratios around 2.0. Consequently, the only difference between the groups involved the number of S^+ received, which, although schedule dependent, are small in comparison to the post-session feeding amounts of rat chow. In the studies that have demonstrated more significant physiological changes, the change in schedule demanded markedly elevated or reduced displays of response rates or numbers, e.g., FR 50 to 125; CRF extinction. Indeed, a recent unpublished study by Valliant [10] showed that rats shifted suddenly from FR 20 to FR 40 or FR 80 displayed highly significant decreases in relative blood lymphocyte numbers (and increases in neutrophils) for at least 7 days.

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